relevant embodiments of the present invention. Applicants reserve the right to pursue claims of similar or differing scope in the future.

Applicants note with appreciation that the claims were found to be free of the art.

Applicants note with appreciation that claims 32, 33, 36, and 44 are allowed.

Applicants now address the Examiner's rejections in the order presented in the previous Office Action dated March 27, 2002.

Rejection of claims 1-27, 29-33, 36, and 38-39 under 35 U.S.C. § 112, first paragraph

Claims 1-27, 29-31, and 38-43 stand rejected under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a manner to enable a skilled artisan to make and use the claimed invention." In particular, the Examiner takes the position that the specification is not enabled in view of: (A) Applicants' claims encompass any mutated MBP; (B) the need to teach in the specification how to identify appropriate mutations in the MBPs; and (C) Applicants' claims drawn to *ex-vivo* gene therapy still encompass in-vivo considerations such as in vivo delivery of the macrolide and the concern that what works on cells in vitro might not work on implanted cells because of the complex environment in vivo. Applicants respectfully traverse this rejection.

(A) First, and without acquiescing to the Examiner's assertion, Applicants have amended independent claims 1, 16, and 36, without disclaimer or prejudice, to focus on aspects of greatest current commercial interest, specifying that the mutated MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin or FKBP:rapamycin associated protein (FRAP). Accordingly, the subject matter of the amended claims is directed to four types of mutated MBPs (i.e., FKBP, cyclophilin, calcineurin, and FRAP) which are amply taught in the specification, as was recognized by the Examiner (for which applicants are appreciative). These amendments are believed to render moot the Examiner's first issue, noted above, and may reduce the scope of some of the other concerns set forth in the Office Action.

(B) Second, we turn to the Examiner's concern that the specification teach how to identify mutations in MBPs appropriate for practice of the invention. Here, we note that the specification explicitly teaches the desired features of the mutations in a mutated MBP and does teach how to select them. For example, the MBP can be engineered with compensatory mutations sufficient to

decrease the dissociation constant (Kd) for binding to the macrolide, relative to the native MBP, preferably by at least 1, 2, 3 or even 5 or more orders of magnitude" (see e.g., page 6, lines 16-20). Second, the specification amply teaches how to make and identify mutations in an MBP that would result in increased binding to the corresponding macrolide (i.e., lowering of the K_d). In a working example (pages 56-58), Applicants teach identification of mutations in cyclophilin (causing decreased binding to the corresponding cyclosporin). In another working example (pages 58-60), Applicants further teach identification of mutations in FKBP (causing decreased binding to the corresponding FK506). Third, the specification teaches how to identify other mutated ligand-binding proteins and ligands binding thereto (see, e.g., pages 18-21), for example, by using modified two-hybrid-type assays and phage display screening. Thus, given the teaching of the specification and the knowledge in the art at the time of this invention, a skilled artisan would in fact readily identify appropriately mutated MBPs.

(C) Third, on the subject of "in vivo considerations", we point out that the delivery of macrolides is discussed on pages 43 (last paragraph) through page 44, and, in fact, was subject matter already well known to the art as of Applicants' effective filing date. The formulation and administration of macrolides such as rapamycin, FK506, and cyclosporin, for example, had been amply reported in the scientific and patent literature by our effective filing date, using a variety of formulations and modes of administration. A search of the USPTO web site revealed that 116 patents issued just between 1991 and 1995 with the terms "rapamycin", "FK506" or "cyclosporin" in their claims. While some of those may not be directly relevant to the issue at hand, it does give some indication of the pre-existing high level of familiarity in the art for administering such compounds in vivo.

Finally, to the extent that this rejection is directed to independent claim 31 which recites an *ex vivo* gene therapy method for reducing GVHD, Applicants note that claim 31 has been canceled, rendering this rejection moot. The remaining pending claims, including claim 16 which recites an *ex vivo* method of gene therapy (but not for reducing GVHD) are believed to be amply enabled for the reasons discussed above. Applicants point out again that various examples in the literature have demonstrated successful transplantation of engineered T cells at the time of the invention, including the Bonini article (provided in the previous response). In view of these successful results from *ex vivo* transplantation of engineered T cells and the teachings of the instant application, a person of skill in the art would reasonably anticipate that a mutated MBP

selected from FKBP, cyclophilin, calcineurin, and FRAP, selected as described in the specification could inhibit T cell function when contacted with a corresponding macrolide. Another illustrative example of successful development of engineered cells ex vivo and introduction of those cells into an animal without loss of the expected function is Magari et al, 1997, J Clin Invest 100(11):2865-2872 (provided as **Exhibit A** in the previous response) as a slightly more recent example involving cells engineered for different purposes than in the present invention. These concrete examples indicate that the Examiner's generalized concerns that the invention would not work in vivo are unfounded. Absent a more particular basis for this ground of rejection, we respectfully request its reconsideration and withdrawal. If these actual examples and our explanation do not overcome that concern, we respectfully suggest that a utility rejection should be issued in place of an enablement rejection, and that the finality of the Office Action be lifted to give applicants an opportunity to respond fully to that ground for rejection.

For the above reasons, Applicants submit that the pending claims are in fact amply enabled by the teachings of the specification when considered in light of the knowledge of one of ordinary skill in the art as of our effective filing date. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 40-43 under 35 U.S.C. § 112, first paragraph

Applicants have deleted claims 40-43 without prejudice or disclaimer. Applicants explicitly reserve the right to prosecute subsequently claims of the same, similar or overlapping scope. This amendment is made not in acquiescence to any position taken by the Examiner, but solely to expedite prosecution of the other claims at this time. In view of this amendment, the rejection of those claims is moot.

In view of all of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Furthermore, in response to the new matter objection raised in the Advisory Action dated October 22, 2002, Applicants respectfully submit that the pending claims as amended are fully supported by the original specification. In particular, the Examiner objects to the term

"preferentially" in claims 1, 16, 18, and 39. Applicants note that this term is used throughout the specification, with reference to binding of a macrolide to a corresponding MBP (see, e.g., page 18, lines 5, 7, 12, and 18). In addition, the Examiner objects to the recitation "inhibiting T cells" under 35 U.S.C. §112, second paragraph. In view of the amendments to the claims, this objection is rendered moot.

CONCLUSION

Applicants appreciate that the Examiner has indicated certain claims as allowable. Applicants believe that the present amendments merely clarify the claimed invention and the pending claims should be considered allowable on the same ground as the Examiner's earlier indication of allowability. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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